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Factors associated with ophtalmological recovery in syphilitic uveitis

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Introduction

It has long been hypothesized that syphilitic uveitis (SU) was closely related to neurosyphilis, and current treatment guidelines recommend to treat it as such. Hence, treatment with intravenous penicillin G (6MUI for 10-14 days) is demanding and may extend the length of hospital stay. While ceftriaxone (CRO), oral amoxicillin plus probenecid, azithromycin, and doxycycline are shown effective for early stages of syphilis, there are few data regarding the safety and efficacy of alternative treatments for neurosyphilis and SU. This work aims to identify predictors of treatment success of SU, and to evaluate the efficacy of alternative therapies.

Methods

A retrospective multicenter study was conducted from January 2003 to April 2016 in two tertiary ophthalmic centers (Cochin and the Quinze-Vingts National Ophthalmology Hospital). Adult patients treated for SU were identified thanks to the medical information system databases. SU was defined by the presence of ocular inflammation compatible with the diagnosis of syphilis, positivity of both serum TPHA and VDRL tests, and the exclusion of alternate diagnoses.

Sociodemographics and Data from ophthalmological examinations at baseline, one week (W1) (8 ± 4 days), one month (M1) (30 ± 12 days), and at last follow-up after antimicrobial treatment onset were collected. As defined by the SUN guidelines, improvement was defined by a ≥ two-step decrease of the levels of both anterior chamber (AC) cells and vitreous haze inflammation, and by chorioretinal lesions' size reduction. Recovery (main outcome measure) was defined as the resolution of inflammation in all anatomic ocular structures.

Results

66 patients (95 eyes) were included in the study. Patients were treated with 18 different regimens that could be merged in four different groups (group A: ≥ 14 days of penicillin G, n= 27; group B:≥ 5 days of penicillin G followed by CRO or benzathine penicillin G (BPG), n=14; group C: Treatment with CRO or BPG, n=8; group D: Oral doxycycline, n=1)

Characteristics	Group A (n=27)	Group B (n=14)	Group C (n=8)	Total (n=49)	p-value
Treating ward					0.01
Infectious Diseases	12 (44)	0	0	12 (24)	
Internal Medicine	12 (44)	14 (100)	8 (100)	34 (70)	
Dermatology	3 (12)	0	0	3 (6)	
Median age, years (IQR)	50 (39-58)	50 (43-55)	51 (40.5-58)	50 (40-56)	0.85
Sex	-	-	-	-	0.28
Male	25 (93)	11 (79)	8 (100)	44 (90)	-
Female	2 (7)	3 (21)	0	5 (10)	-
HIV status	-	-	-	-	0.31
Negative	16 (59)	5 (36)	3 (37)	24 (49)	-
Positive	11 (41)	9 (64)	5 (63)	25 (51)	-
Median CD4, cells/mm³ (IQR) *	312 (150-617)	296 (187-361)	250 (56-514)	296 (150-514)	0.84
CD4 > 200/mm³ *	8 (73)	6 (67)	3 (60)	17 (68)	1.0
Past history of syphilis	0	3 (21)	0	3 (6)	0.02
Other concomitant active STD(s) at baseline	2/26 (8)	4/14 (29)	1/7 (14)	7/47 (15)	0.18
Prior syphilitic canker	9/27 (33)	6/11 (55)	3/7 (42)	18/45 (40)	0.53
Cutaneous manifestations in the year before diagnosis of SU	17 (63)	7 (63)	5 (71)	29 (64)	1.0
Syphilitic roseola	12/27 (44)	5/11 (45)	3/7 (43)	20/45 (44)	1.0
Syphilids	14/27 (52)	7/11 (64)	2/8 (25)	23/46 (50)	0.31
Median duration between onset of cutaneous and ocular symptoms, days (IQR)	1.0 [0.5-3.0]	2.0 [0-7.0]	2 [0-2.0]	1.5 [0.5-3.0]	0.81
Median duration between onset of ocular symptoms and first evaluation, days, (IQR)	19 (4-43)	21 (4-31)	6 (4-15)	15 (4-33)	0.55
Bilateral ocular involvement	12 (46)	7 (50)	2 (25)	21 (44)	0.62
Neurological symptoms attributable to syphilis	5/21 (24)	1/11 (9)	0	6/36 (17)	0.55
Liver cytolysis	1/26 (4)	2/14 (14)	0	3/47 (6)	0.24
Median VRDL, UI/ml (IQR)	32 (32-64)	128 (64-256)	128 (32-256)	64 (32-128)	0.10
LP performed	25 (93)	12 (86)	4 (50)	41 (84)	0.03
Abnormal LP ¶	22 (88)	9 (75)	3 (75)	34 (83)	0.62
Pleiocytosis (>10/mm³)	15 (60)	5 (42)	3 (75)	23 (56)	0.57
Hyperproteinorrachia (>0.4 g/L)	18 (72)	8 (67)	2 (50)	28 (68)	0.69
Microbiological documentation **	16 (64)	4 (33)	3 (75)	23 (56)	0.12

Table 1. Patients' baseline characteristics according to treatment regimens (n=49)

Results

Overall, complete recovery was reported in 46 (65%) eyes at M1, with a trend towards higher recovery rates in eyes from group B (55% vs. 86% vs. 60%, p=0.06), without difference between those treated with ceftriaxone or BPG (recovery at M1: 15/18 and 3/3 eyes respectively, p=1.0).

At last follow-up, overall recovery was reported in 60 (85%) eyes, without any difference between treatment groups (p=0.20) and baseline ophthalmological findings.

Characteristics	Group A (n=40)	Group B (n=21)	Group C (n=10)	Total (n=71)	p-value
Visual acuity					0.01
<2/10	16 (40)	1 (5)	1 (10)	18 (25)	-
2/10-5/10	9 (23)	8 (38)	6 (60)	23 (32)	-
>5/10	15 (37)	12 (57)	3 (30)	30 (43)	-
Median IOT, mmHg (IQR)	13 [11-15]	12.5 [10.5-14]	11.5 [10-17]	13 [11-15]	0.38
Anatomic location of ocular inflammation					
Isolated anterior uveitis	4 (10)	5 (23)	1 (10)	10 (14)	0.40
Isolated intermediate uveitis	0	2 (10)	0	2 (3)	0.19
Isolated posterior uveitis	23 (58)	3 (14)	3 (30)	29 (41)	0.003
Isolated papillitis	11/23 (48)	2/3 (67)	3/3 (100)	16 (55)	-
Retinitis (or chorioretinitis) with papillitis	10 /23 (43)	1/3 (33)	0	11 (38)	-
Retinitis (or chorioretinitis) without papillitis	2/23 (9)	0	0	2 (7)	-
Panuveitis	13 (33)	11 (52)	6 (60)	30 (42)	0.18
Crystalline lens					1.0
Clear	39 (98)	21 (100)	10 (100)	70 (99)	-
Cataract	1 (2)	0	0	1 (1)	-
Pseudophakia	0	0	0	0	-
AC cells					0.02
]0.5-2]	13 (33)	12 (57)	1 (10)	26 (37)	-
[3-4]	7 (18)	6 (29)	4 (40)	17 (24)	-
Hypopion	2 (5)	2 (10)	0	4 (6)	0.79
Median Flare, photons/ms (IQR)	37.9 [13.4-57.4]	23.5 [14-64.8]	162 .2 [7.7-185]	33 [13-64.8]	0.60
Vitreous haze					0.31
]0.5-2]	15 (41)	12 (57)	4 (50)	31 (47)	-
[3-4]	2 (5)	3 (14)	1 (13)	6 (9)	-
Ocular complications					
Ocular hypertension	0	0	0	0	-
Posterior synechiae	8 (20)	3 (14)	2 (20)	13 (18)	0.90
Serous retinal detachment	4 (10)	0	0	4 (6)	0.44
Cystoid macular edema	0	1 (5)	0	1 (2)	0.47
Glaucoma	0	0	0	0	-
Retinal vasculitis (fundoscopy)	4 (10)	4 (19)	2 (20)	10 (14)	0.50
Prior treatment with anti-treponemal drugs	5 (12)	4 (19)	1 (10)	10 (14)	0.90
Topical glucocorticoids	19 (49)	12 (57)	6 (60)	37 (53)	0.75
Eye drops	17 (44)	14 (67)	5 (50)	36 (51)	0.21
Periocular dexamethasone injections	5 (13)	1 (5)	1 (10)	7 (10)	0.75
Systemic glucocorticoids					
Methylprednisolone pulses (followed by oral prednisone)	3 (8)	1 (5)	1 (10)	5 (7)	1.0
Oral prednisone (not preceded by methylprednisolone pulses)	10 (25)	2 (10)	3 (30)	15 (21)	0.26

Table 2. Baseline ophthalmological findings according to treatment regimens (n=71 eyes)

Results

In univariate analysis, ≥2/10 of baseline visual acuity (crude OR: 3.4 95%CI[1.2-9.7]; p=0.02) and early improvement at W1 (crude OR: 14 [3.8 – 51.6]; p=0.001) were significantly associated with recovery at M1 but age, sex, HIV status, delay between onset of visual symptoms and baseline ophthalmological evaluation, uveitides' subtypes, high ocular inflammation, VDRL titer, type of antibiotic regimen, and use of either glucocorticoid eye drops or oral prednisone were not. Conversely, the use of periocular dexamethasone injections and methylprednisolone pulses were significantly associated with treatment failure.

In the final multivariate model, after adjusting for the initial visual acuity and the antimicrobial treatment regimen, clinical improvement at W1 (corrected RR: 3.5 (2.3 – 3.8); p=0.001) was the only predictive factor of recovery at M1, while the use of periocular dexamethasone injections (cRR: 0.05 [0.02 – 0.6]; p=0.01) and methylprednisolone pulses (no treatment success in patients who received pulses) negatively affected eyes' outcomes.

Conclusion

Rather than the antimicrobial drug used, early improvement seems to best predict ophthalmological recovery. These findings suggest that selected patients with early favorable clinical course after onset of penicillin G could be safely switched to an alternative antibiotic regimen.

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